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EXAMINER	
CROW, ROBERT THOMAS	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/750,315	BERLIN ET AL.	
	Examiner	Art Unit	
	Robert T. Crow	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,20-23,36,38-41,43-45 and 47-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18, 20-23, 36, 38-41, 43-45, and 47-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

Status of the Claims

1. This action is in response to papers filed 6 June 2008 in which claims 18, 20, 23, 36, 38, 41, 43, 45, and 47 were amended, claims 19, 37, 42, and 46 were canceled, and new claims 53-55 were added. All of the amendments have been thoroughly reviewed and entered.

The interview summary is acknowledged and the interview record is complete.

The objections to the claims listed in the previous Office Action are withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. 112, first paragraph, are withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. 112, second paragraph, are withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections necessitated by the amendments.

In view of Applicant's request on pages 14-15 of the Remarks filed 6 June 2008 (hereafter "the Remarks") that the request for a terminal disclaimer be held in abeyance, the previous rejections under the judicially created doctrine of obviousness-type double patenting over the claims of copending Application No. 11/753,361 are maintained.

Claims 18, 20-23, 36, 38-41, 43-45, and 47-55 are under prosecution.

2. The following rejections are new rejections necessitated by the amendments.

Claim Rejections - 35 USC § 112, First Paragraph-New Matter

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 55 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This is a new matter rejection. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 55 requires "a mixer operably coupled to the reaction chamber." Applicant cites paragraph 0033 of the instant specification for support of new claim 55. While paragraph 0033 states that nucleotides "can be allowed to equilibrate between the different parts of the reaction chamber by passive diffusion or active mixing processes," that paragraph merely teaches "active mixing **processes**;" i.e., **methods** of mixing. A review of the specification yields no recitation of the claimed **structural** limitation of a "mixer" nor any recitation of any type of mixing device operably coupled to the reaction chamber. Therefore, the instantly claimed "mixer operably coupled to the reaction chamber" constitutes new matter.

Claim Rejections - 35 USC § 112, Second Paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 53-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 53-55 are indefinite in claim 53, which recites the limitation "the first or second Raman detection unit" in line 11 of claim 53. The limitation "the first or second Raman detection unit" lacks antecedent basis because the claim does not previously recite a **second** Raman detection unit. It is suggested that the claim be amended to reflect proper antecedent basis.

It is also noted, solely for Applicant's convenience, that depended claim 54 recites "a second Raman detection unit" in line 1. Thus, any amendments to claim 53 should also take into account the second Raman detection unit of claim 54.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 18, 20-22, 36, 38-39, 41, 43-45, and 47-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shipwash (U.S. Patent Application Publication No. US 2002/0058273 A1, published 16 May 2002) in view of Davis (U.S. Patent Application Publication No US 2002/0102595 A1, published 1 August 2002) in view of Chan et al (U.S. Patent Application No. US 2003/0187237 A1, published 2 October 2003, filed 26 March 2002).

Regarding claims 18 and 49, Shipwash teaches an apparatus. In a single exemplary embodiment, Shipwash teaches a reaction chamber containing a single template nucleic acid molecule attached to an immobilization surface; namely, a mixing channel, which is a reaction chamber, further comprising a bead having nucleic acids immobilized thereon (Figures 11 and 14, and paragraphs 0066 and 0255). The apparatus of Shipwash further comprises an inlet channel in fluid communication with the reaction chamber; namely, Figure 11, wherein the inlet channel comprises the

channel having the digestion chamber (Figure 11), which is separate and distinct from the reaction chamber because the chamber is separate (paragraph 0043). Shipwash also teaches the apparatus comprises a separate and distinct outlet channel in fluid communication with the reaction chamber; namely, Figure 9, wherein the outlet channel is separate and downstream of the reaction chamber.

Shipwash also teaches a first Raman detection unit operably coupled to the inlet channel; namely, an optical detector is integrated onto the inlet digestion chamber (paragraph 0484), wherein Raman spectroscopy is used (paragraph 0174); thus, the first optical detector is a Raman detection unit. Shipwash also teaches a second Raman detection unit operably coupled to the outlet channel; namely, a second detector is coupled to the outlet of Figure 9. The second detector is a Raman spectrophotometer and Raman spectroscopy is used (paragraphs 0224 and 0174). The first and second detectors are therefore distinct and separate from the reaction chamber and are positioned before and after the reaction chamber. Shipwash also teaches the apparatus further comprises a mesh in the form of filters and grids that retain nanoparticles in the channels of the apparatus (paragraphs 0167 and 0270). While Shipwash does not specifically teach the mesh is in the outlet channel; the courts have held that the rearrangement of parts within a device is obvious when the arrangement does not specifically modify the operation of the device (*In re Japikse*, 181 F.2d 1019, 86 USPQ 70 (CCPA 1950)). See MPEP §2144.04. Shipwash also teaches the concentrations of nucleotides are measured by Raman spectroscopy as they flow through the inlet channel and the outlet channel; namely, the system detects concentration (paragraph

0031) and uses Raman spectroscopy (paragraph 0174). Thus, each Raman detector detects concentration in its respective (i.e., inlet or outlet) channel.

It is noted that the courts have held that "while features of an apparatus may be recited either structurally or functionally, claims directed to an apparatus must be distinguished from the prior art in terms of structure rather than function." *In re Schreiber*, 128 F.3d 1473, 1477-78, 44 USPQ2d 1429, 1431-32 (Fed. Cir. 1997). In addition, "[A]pparatus claims cover what a device *is*, not what a device *does*." *Hewlett-Packard Co. v. Bausch &Lomb Inc.*, 909 F.2d 1464, 1469, 15 USPQ2d 1525, 1528 (Fed. Cir. 1990) (emphasis in original). Therefore, the various uses recited in claim 18 (e.g., measuring concentration of nucleotides) fail to define additional structural elements to the device of claim 18. Because the prior art teaches the structural elements of claim 18, the claim is obvious over the prior art.

While Shipwash also teaches detection of binding to an oligonucleotide aptamer (paragraph 0155), Shipwash does not teach first and second concentrations of nucleotides in the inlet and outlet channels or a non-aptameric nucleic acid (i.e., claim 18), or a polymerase and primer (i.e., claim 49).

However, Davis teaches an apparatus comprising a reaction chamber containing a template comprising nucleic acid molecule attached to an immobilization surface; namely, an immobilized complex comprising a target (i.e., non-aptameric) nucleic acid, a primer nucleic acid, and a nucleic acid polymerase (paragraph 0012). The immobilized complex is contained within a sample (i.e., reaction) chamber (i.e., claim 49; paragraph 0057). Davis also teaches the target nucleic acid is subjected to

sequencing by adding and detecting nucleotides upstream of the immobilized complex and detecting the presence of absence of the nucleotides downstream from the immobilized complex, and that the concentrations of the nucleotides (i.e., NTPs) are tracked (paragraph 0006-0009); thus, upon incorporation of a nucleotide using the immobilized nucleic acid, polymerase and primer, a different (i.e., second) concentration of nucleotide is detected compared to the original (i.e., first) concentration of nucleotide detected upstream. The concentration difference is proportional to the amount of nucleotide incorporated into a newly synthesized strand because a polymerase extends a primer using the nucleotides (paragraph 0006-0009). Davis also teaches first and second illumination zones that are respectively upstream and downstream of the immobilized complex (paragraph 0006), wherein the first and second illumination zones each have a detection device operably coupled thereto (claim 15 of Davis). The detectors are configured to perform Raman spectroscopy because Raman scattering labels are detected (paragraph 0054). Davis also teaches the first and second concentration of nucleotides and the immobilized nucleic acid provide the added advantage of allowing genotyping of the target nucleic acid (paragraph 0052), which aids in the detection of genetic diseases. Thus, Davis teaches the known technique of using immobilized nucleic acids and first and second concentrations of nucleotides in the upstream and downstream of the immobilized nucleic acid (i.e., claim 18) and a non-aptameric nucleic acid, primer, and polymerase immobilized in the chamber (i.e., claim 49).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising immobilized nucleic acids as taught by Shipwash so that the device comprises the immobilized non-aptameric nucleic acid, polymerase, and primer (i.e., claim 49) and the two different upstream and downstream concentrations of nucleotides (i.e., claim 18) as taught by Davis. The modification would result in the first concentration of nucleotide being detected upstream of the reaction chamber and the second concentration being detected downstream of the reaction chamber as taught by Davis; thus, because the first Raman detector of Shipwash is coupled to the inlet channel and the second Raman detector of Shipwash is coupled to the outlet channel, the modification results in the first and second concentrations being in the inlet and outlet channels, respectively, thus arriving at the claimed apparatus with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in an apparatus having the added advantage of aiding in the detection of genetic diseases as a result of allowing genotyping of the unknown target nucleic acid as explicitly taught by Davis (paragraph 0054). In addition, it would have been obvious to the ordinary artisan that the known technique of using the nucleic acids, nucleotide concentrations, and polymerase and primer of Davis could have been applied to the apparatus of Shipwash with predictable results because the known technique of using the nucleic acids, nucleotide concentrations, and polymerase and primer of Davis predictably result in immobilized molecules suitable for analysis for genetic diseases.

Shipwash also teaches each Raman detection unit is capable of detecting at least one nucleotide at the single molecule level; namely, single molecule detection is performed (paragraph 0168). Nucleotides are molecules; thus, because single molecule detection is performed, and because nucleotides are molecules, Shipwash teaches a unit capable of detecting a nucleotide at the single molecule level. However, Neither Shipwash nor Davis teach the Raman detection units configured for surface enhanced Raman spectroscopy or the detection of at least one unlabeled nucleotide at a single nucleotide level.

However, Chan et al teaches Raman detection units configured for surface enhanced Raman spectroscopy of nucleotides (paragraph 0072), wherein the detection units detect single unlabeled nucleotides, wherein the detectors have the added advantage of specifically identifying the nucleotide (paragraph 0096) for the purpose of sequencing a nucleic acid (Abstract), which aids in the detection of genetic diseases. Thus, Chan et al teach the known technique of using detection units configured for surface enhanced Raman spectroscopy detection of single unlabeled nucleotides.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising two Raman detection units of Shipwash in view of Davis so that the detection units are the detection units configured for surface enhanced Raman spectroscopy detection of single unlabeled nucleotides as taught by Chan et al to arrive at the instantly claimed apparatus with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have

resulted in an apparatus having the added advantage of aiding in the detection of genetic diseases as a result of allowing specific identification of a nucleotide) for the purpose of sequencing a nucleic acid as taught by Chan et al (Abstract and paragraph 0096). In addition, it would have been obvious to the ordinary artisan that the known detection units of Chan et al could have been used as the detection units in the apparatus of Shipwash in view of Davis with predictable results because the known detection units of Chan et al predictably result in detectors usable for detecting biological molecules.

Regarding claim 20, the apparatus of claim 18 is discussed above. Shipwash also teaches the concentrations of nucleotides are measured by Raman spectroscopy as they flow through the inlet channel and the outlet channel; namely, the system detects concentration (paragraph 0170) and uses Raman spectroscopy (paragraph 0174).

In addition, as noted above, apparatus claims cover what a device *is*, not what a device *does*. Therefore, the various uses recited in claim 20 (e.g., measuring concentration of nucleotides) fail to define additional structural elements to the device of claim 20. Because the prior art teaches the structural elements of claim 20, the claim is obvious over the prior art.

Regarding claim 21, the apparatus of claim 18 is discussed above. Shipwash teaches nucleic acids are on metal particles in channels (paragraph 0043), which is interpreted as being in the inlet and outlet channels. Shipwash does not explicitly teach surface enhanced Raman spectroscopy active particles that are not labels.

However, Chan et al teach channels packed with SERS nanoparticles (Abstract), which have the added advantage of enhancing the detection of the Raman signal from the nucleotides (paragraph 0010). Thus, Chan et al teach the known technique of using channels packed with SERS nanoparticles.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus of Shipwash in view of Davis and Chan et al so that inlet and outlet channels each comprise SERS nanoparticles of Chan et al to arrive at the instantly claimed apparatus with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in an apparatus having the added advantage of enhancing the detection of the Raman signal from the nucleotides as taught by Chan et al (paragraph 0010). In addition, it would have been obvious to the ordinary artisan that the known technique of having channels packed with SERS nanoparticles detection units as taught by Chan et al could have been applied to the apparatus of Shipwash in view of Davis and Chan et al with predictable results because known technique of having channels packed with SERS nanoparticles detection units as taught by Chan et al predictably result in channel configurations useful for detecting nucleotides.

Regarding claim 22, the apparatus of claim 18 is discussed above. Shipwash also teaches the inlet channel and outlet channel diameter is between about 100 and about 200 micrometers in diameter (paragraph 0210).

Regarding claims 36 and 50, Shipwash teaches an apparatus. In a single exemplary embodiment, Shipwash teaches a reaction chamber containing a single template nucleic acid molecule attached to an immobilization surface; namely, a mixing channel, which is a reaction chamber, further comprising a bead having nucleic acids immobilized thereon (Figures 11 and 14, and paragraphs 0066 and 0255). The apparatus of Shipwash further comprises an inlet channel in fluid communication with the reaction chamber; namely, Figure 11, wherein the inlet channel comprises the channel having the digestion chamber (Figure 11), which is separate and distinct from the reaction chamber because the chamber is separate (paragraph 0043). Shipwash also teaches the apparatus comprises a separate and distinct outlet channel in fluid communication with the reaction chamber; namely, Figure 9, wherein the outlet channel is separate and downstream of the reaction chamber.

Shipwash also teaches a first Raman detection unit operably coupled to the inlet channel; namely, an optical detector is integrated onto the inlet digestion chamber (paragraph 0484), wherein Raman spectroscopy is used (paragraph 0174); thus, the first optical detector is a Raman detection unit. Shipwash also teaches a second Raman detection unit operably coupled to the outlet channel; namely, a second detector is coupled to the outlet of Figure 9. The second detector is a Raman spectrophotometer and Raman spectroscopy is used (paragraphs 0224 and 0174). The first and second detectors are therefore distinct and separate from the reaction chamber and are positioned before and after the reaction chamber. Shipwash also teaches the apparatus further comprises a mesh in the form of filters and grids that retain nanoparticles in the

channels of the apparatus (paragraphs 0167 and 0270). While Shipwash does not specifically teach the mesh is in the outlet channel; the courts have held that the rearrangement of parts within a device is obvious when the arrangement does not specifically modify the operation of the device. Shipwash also teaches the concentrations of nucleotides are measured by Raman spectroscopy as they flow through the inlet channel and the outlet channel; namely, the system detects concentration (paragraph 0031) and uses Raman spectroscopy (paragraph 0174). Thus, each Raman detector detects concentration in its respective (i.e., inlet or outlet) channel.

As noted above, apparatus claims cover what a device *is*, not what a device *does*. In particular, it is noted that claim 36 does not actually require first and second concentrations of nucleotides in the inlet and outlet channels, respectively. Therefore, the limitation "wherein a difference between a first concentration of nucleotide in the inlet channel and a second concentration of nucleotide in the outlet channel is proportional to the amount of nucleotide incorporated into a newly synthesized strand complementary to the nucleic acid molecule in the reaction chamber" constitutes an intended use of the claimed apparatus. Because the various uses recited in claim 36 (e.g., measuring concentration of nucleotides) fail to define additional structural elements to the device of claim 36, the claim is obvious over the prior art.

While Shipwash also teaches detection of binding to an oligonucleotide aptamer (paragraph 0155), Shipwash does not teach a newly synthesized strand complementary

to a non-aptameric nucleic acid molecule in the chamber (i.e., claim 36) or a polymerase and primer (i.e., claim 50).

However, Davis teaches an apparatus comprising a reaction chamber containing a template comprising nucleic acid molecule attached to an immobilization surface; namely, an immobilized complex comprising a target (i.e., non-aptameric) nucleic acid, a primer nucleic acid, and a nucleic acid polymerase (paragraph 0012). The immobilized complex is contained within a sample (i.e., reaction) chamber (i.e., claim 50; paragraph 0057). Davis also teaches the target nucleic acid is subjected to sequencing by adding and detecting nucleotides upstream of the immobilized complex and detecting the presence of absence of the nucleotides downstream from the immobilized complex, and that the concentrations of the nucleotides (i.e., NTPs) are tracked (paragraph 0006-0009).Davis also teaches detectors configured to perform Raman spectroscopy because Raman scattering labels are detected (paragraph 0054). Davis also teaches the immobilized nucleic acid provides the added advantage of allowing genotyping of the target nucleic acid (paragraph 0052), which aids in the detection of genetic diseases. Thus, Davis teaches the known technique of using immobilized non-aptameric nucleic acids (i.e., claim 36) and a polymerase and primer (i.e., claim 50).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising immobilized nucleic acids as taught by Shipwash so that the device comprises the immobilized non-aptameric nucleic acid (i.e., claim 36) and the polymerase and primer

in the chamber (i.e., claim 50) as taught by Davis to arrive at the claimed apparatus with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in an apparatus having the added advantage of aiding in the detection of genetic diseases as a result of allowing genotyping of the unknown target nucleic acid as explicitly taught by Davis (paragraph 0054). In addition, it would have been obvious to the ordinary artisan that the known technique of using the nucleic acids, polymerase, and primer of Davis could have been applied to the apparatus of Shipwash with predictable results because the known technique of using the nucleic acids, polymerase, and primer of Davis predictably results in immobilized molecules suitable for analysis for genetic diseases.

Shipwash also teaches each Raman detection unit is capable of detecting at least one nucleotide at the single molecule level; namely, single molecule detection is performed (paragraph 0168). Nucleotides are molecules; thus, because single molecule detection is performed, and because nucleotides are molecules, Shipwash teaches a unit capable of detecting a nucleotide at the single molecule level. Shipwash also teaches nucleic acids are on metal particles in channels (paragraph 0043), which is interpreted as being in the inlet and outlet channels. However, neither Shipwash nor Davis teach the Raman detection units configured for surface enhanced Raman spectroscopy or the detection of at least one unlabeled nucleotide at a single nucleotide level, nor do Shipwash or Davis teach surface enhanced Raman spectroscopy active particles that are not labels.

However, Chan et al teaches Raman detection units configured for surface enhanced Raman spectroscopy of nucleotides (paragraph 0072), wherein the detection units detect single unlabeled nucleotides, wherein the detectors have the added advantage of specifically identifying the nucleotide (paragraph 0096) for the purpose of sequencing a nucleic acid (Abstract), which aids in the detection of genetic diseases. Chan et al teach channels packed with SERS nanoparticles (Abstract), which have the added advantage of enhancing the detection of the Raman signal from the nucleotides (paragraph 0010). Thus, Chan et al teach the known technique of using detection units configured for surface enhanced Raman spectroscopy detection of single unlabeled nucleotides and the known technique of using channels packed with SERS nanoparticles.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising two Raman detection units of Shipwash in view of Davis so that the detection units are the detection units configured for surface enhanced Raman spectroscopy detection of single unlabeled nucleotides, and so that the channels comprise SERS nanoparticles as taught by Chan et al to arrive at the instantly claimed apparatus with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in an apparatus having the added advantage of aiding in the detection of genetic diseases as a result of allowing specific identification of a nucleotide) for the purpose of sequencing a nucleic acid as taught by Chan et al (Abstract and paragraph 0096), as well as having the

additional added advantage of enhancing the detection of the Raman signal from the nucleotides as taught by Chan et al (paragraph 0010). In addition, it would have been obvious to the ordinary artisan that the known detection units and SERS nanoparticle packed channels of Chan et al could have been used in the apparatus of Shipwash in view of Davis with predictable results because the known detection units and SERS nanoparticle packed channels of Chan et al predictably result in detectors and channels usable for detecting nucleotides.

Regarding claim 38, the apparatus of claim 36 is discussed above. Shipwash also teaches the concentrations of nucleotides are measured by Raman spectroscopy as they flow through the inlet channel and the outlet channel; namely, the system detects concentration (paragraph 0170) and uses Raman spectroscopy (paragraph 0174).

In addition, as noted above, apparatus claims cover what a device *is*, not what a device *does*. Therefore, the various uses recited in claim 38 (e.g., measuring concentration of nucleotides) fail to define additional structural elements to the device of claim 38. Because the prior art teaches the structural elements of claim 38, the claim is obvious over the prior art.

Regarding claim 39, the apparatus of claim 36 is discussed above. Shipwash also teaches the inlet channel and outlet channel diameter is between about 100 and about 200 micrometers in diameter (paragraph 0210).

Regarding claims 41 and 51, Shipwash teaches an apparatus. In a single exemplary embodiment, Shipwash teaches a reaction chamber containing a single

template nucleic acid molecule attached to an immobilization surface; namely, a mixing channel, which is a reaction chamber, further comprising a bead having nucleic acids immobilized thereon (Figures 11 and 14, and paragraphs 0066 and 0255). The apparatus of Shipwash further comprises an inlet channel in fluid communication with the reaction chamber; namely, Figure 9, wherein the inlet channel comprises the channel having the digestion chamber (Figure 9), which is separate and distinct from the reaction chamber because the chamber is separate (paragraph 0043). Shipwash also teaches the apparatus comprises a separate and distinct outlet channel in fluid communication with the reaction chamber; namely, Figure 9 show an outlet channel is separate and downstream of the reaction chamber.

Shipwash also teaches a first Raman detection unit operably coupled to the inlet channel; namely, an optical detector is integrated onto the inlet digestion chamber (paragraph 0484), wherein Raman spectroscopy is used (paragraph 0174); thus, the first optical detector is a Raman detection unit. Shipwash also teaches a second Raman detection unit operably coupled to the outlet channel; namely, a second detector is coupled to the outlet of Figure 9. The second detector is a Raman spectrophotometer and Raman spectroscopy is used (paragraphs 0224 and 0174). The first and second detectors are therefore distinct and separate from the reaction chamber and are positioned before and after the reaction chamber. Shipwash also teaches the apparatus further comprises a mesh in the form of filters and grids that retain nanoparticles in the channels of the apparatus (paragraphs 0167 and 0270). While Shipwash does not specifically teach the mesh is in the outlet channel; the courts have

held that the rearrangement of parts within a device is obvious when the arrangement does not specifically modify the operation of the device. Shipwash also teaches the concentrations of nucleotides are measured by Raman spectroscopy as they flow through the outlet channel; namely, the system detects concentration (paragraph 0031) and uses Raman spectroscopy (paragraph 0174).

As noted above, apparatus claims cover what a device *is*, not what a device *does*. In particular, it is noted that claim 41 does not actually require first and second concentrations of nucleotides in the inlet and outlet channels, respectively. Therefore, the limitation "wherein a difference in nucleotide concentration measured with the first Raman detection unit and the second Raman detection unit is proportional to the amount of nucleotide that has been incorporated into a newly synthesized strand complementary to the nucleic acid molecule" constitutes an intended use of the claimed apparatus. Because the various uses recited in claim 41 (e.g., measuring concentration of nucleotides) fail to define additional structural elements to the device of claim 41, the claim is obvious over the prior art.

While Shipwash also teaches detection of binding to an oligonucleotide aptamer (paragraph 0155), Shipwash does not teach a newly synthesized strand complementary to a non-aptameric nucleic acid molecule in the chamber (i.e., claim 41) or a polymerase and primer (i.e., claim 51).

However, Davis teaches an apparatus comprising a reaction chamber containing a template comprising nucleic acid molecule attached to an immobilization surface; namely, an immobilized complex comprising a target (i.e., non-aptameric) nucleic acid,

a primer nucleic acid, and a nucleic acid polymerase (paragraph 0012). The immobilized complex is contained within a sample (i.e., reaction) chamber (i.e., claim 50; paragraph 0057). Davis also teaches the target nucleic acid is subjected to sequencing by adding and detecting nucleotides upstream of the immobilized complex and detecting the presence of absence of the nucleotides downstream from the immobilized complex, and that the concentrations of the nucleotides (i.e., NTPs) are tracked (paragraph 0006-0009).Davis also teaches detectors configured to perform Raman spectroscopy because Raman scattering labels are detected (paragraph 0054). Davis also teaches the immobilized nucleic acid provides the added advantage of allowing genotyping of the target nucleic acid (paragraph 0052), which aids in the detection of genetic diseases. Thus, Davis teaches the known technique of using immobilized non-aptameric nucleic acids (i.e., claim 41) and a polymerase and primer (i.e., claim 51).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising immobilized nucleic acids as taught by Shipwash so that the device comprises the immobilized non-aptameric nucleic acid (i.e., claim 41) and the polymerase and primer in the chamber (i.e., claim 51) as taught by Davis to arrive at the claimed apparatus with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in an apparatus having the added advantage of aiding in the detection of genetic diseases as a result of allowing genotyping of the unknown target nucleic acid as explicitly taught by Davis

(paragraph 0054). In addition, it would have been obvious to the ordinary artisan that the known technique of using the nucleic acids, polymerase, and primer of Davis could have been applied to the apparatus of Shipwash with predictable results because the known technique of using the nucleic acids, polymerase, and primer of Davis predictably results in immobilized molecules suitable for analysis for genetic diseases.

Shipwash also teaches each Raman detection unit is capable of detecting at least one nucleotide at the single molecule level; namely, single molecule detection is performed (paragraph 0168). Nucleotides are molecules; thus, because single molecule detection is performed, and because nucleotides are molecules, Shipwash teaches a unit capable of detecting a nucleotide at the single molecule level. However, Neither Shipwash nor Davis teach the Raman detection units configured for surface enhanced Raman spectroscopy or the detection of at least one unlabeled nucleotide at a single nucleotide level.

However, Chan et al teaches Raman detection units configured for surface enhanced Raman spectroscopy of nucleotides (paragraph 0072), wherein the detection units detect single unlabeled nucleotides, wherein the detectors have the added advantage of specifically identifying the nucleotide (paragraph 0096) for the purpose of sequencing a nucleic acid (Abstract), which aids in the detection of genetic diseases. Thus, Chan et al teach the known technique of using detection units configured for surface enhanced Raman spectroscopy detection of single unlabeled nucleotides.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising two

Raman detection units of Shipwash in view of Davis so that the detection units are the detection units configured for surface enhanced Raman spectroscopy detection of single unlabeled nucleotides as taught by Chan et al to arrive at the instantly claimed apparatus with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in an apparatus having the added advantage of aiding in the detection of genetic diseases as a result of allowing specific identification of a nucleotide) for the purpose of sequencing a nucleic acid as taught by Chan et al (Abstract and paragraph 0096). In addition, it would have been obvious to the ordinary artisan that the known detection units of Chan et al could have been used as the detection units in the apparatus of Shipwash in view of Davis with predictable results because the known detection units of Chan et al predictably result in detectors usable for detecting biological molecules.

Regarding claim 43, the apparatus of claim 41 is discussed above. Shipwash also teaches the concentrations of nucleotides are measured by Raman spectroscopy as they flow through the inlet channel and the outlet channel; namely, the system detects concentration (paragraph 0170) and uses Raman spectroscopy (paragraph 0174).

In addition, as noted above, apparatus claims cover what a device *is*, not what a device *does*. Therefore, the various uses recited in claim 43 (e.g., measuring concentration of nucleotides) fail to define additional structural elements to the device of

claim 43. Because the prior art teaches the structural elements of claim 43, claim 43 is obvious over the prior art.

Regarding claim 44, the apparatus of claim 41 is discussed above. Shipwash also teaches the inlet channel and outlet channel diameter is between about 100 and about 200 micrometers in diameter (paragraph 0210).

Regarding claims 45 and 52, Shipwash teaches an apparatus. In a single exemplary embodiment, Shipwash teaches a reaction chamber containing a single template nucleic acid molecule attached to an immobilization surface; namely, a mixing channel, which is a reaction chamber, further comprising a bead having nucleic acids immobilized thereon (Figures 11 and 14, and paragraphs 0066 and 0255). The apparatus of Shipwash further comprises an inlet channel in fluid communication with the reaction chamber; namely, Figure 9, wherein the inlet channel comprises the channel having the digestion chamber (Figure 9), which is separate and distinct from the reaction chamber because the chamber is separate (paragraph 0043). Shipwash also teaches the apparatus comprises a separate and distinct outlet channel in fluid communication with the reaction chamber; namely, Figure 9 show an outlet channel is separate and downstream of the reaction chamber.

Shipwash also teaches a first Raman detection unit operably coupled to the inlet channel; namely, an optical detector is integrated onto the inlet digestion chamber (paragraph 0484), wherein Raman spectroscopy is used (paragraph 0174); thus, the first optical detector is a Raman detection unit. Shipwash also teaches the apparatus further comprises a mesh in the form of filters and grids that retain nanoparticles in the

channels of the apparatus (paragraphs 0167 and 0270). While Shipwash does not specifically teach the mesh is in the outlet channel; the courts have held that the rearrangement of parts within a device is obvious when the arrangement does not specifically modify the operation of the device. Shipwash also teaches a second Raman detection unit operably coupled to the outlet channel; namely, a second detector is coupled to the outlet of Figure 9. The second detector is a Raman spectrophotometer and Raman spectroscopy is used (paragraphs 0224 and 0174). The first and second detectors are therefore distinct and separate from the reaction chamber and are positioned before and after the reaction chamber. Shipwash also teaches the concentrations of nucleotides are measured by Raman spectroscopy as they flow through the outlet channel; namely, the system detects concentration (paragraph 0031) and uses Raman spectroscopy (paragraph 0174).

As noted above, apparatus claims cover what a device *is*, not what a device *does*. In particular, it is noted that claim 45 does not actually require first and second concentrations of nucleotides in the inlet and outlet channels, respectively. Therefore, the limitation "wherein a difference in nucleotide concentration is proportional to the amount of nucleotide that has been incorporated into a newly synthesized strand complementary to the nucleic acid molecule" constitutes an intended use of the claimed apparatus. Because the various uses recited in claim 45 (e.g., measuring concentration of nucleotides) fail to define additional structural elements to the device of claim 45, the claim is obvious over the prior art.

While Shipwash also teaches detection of binding to an oligonucleotide aptamer (paragraph 0155), Shipwash does not teach a non-aptameric immobilized nucleic acid (i.e., claim 45) or a polymerase and primer (i.e., claim 52).

However, Davis teaches an apparatus comprising a reaction chamber containing a template comprising nucleic acid molecule attached to an immobilization surface; namely, an immobilized complex comprising a target (i.e., non-aptameric) nucleic acid (i.e., claim 45), a primer nucleic acid, and a nucleic acid polymerase (paragraph 0012). The immobilized complex is contained within a sample (i.e., reaction) chamber (i.e., claim 52; paragraph 0057). Davis also teaches the target nucleic acid is subjected to sequencing by adding and detecting nucleotides upstream of the immobilized complex and detecting the presence of absence of the nucleotides downstream from the immobilized complex, and that the concentrations of the nucleotides (i.e., NTPs) are tracked (paragraph 0006-0009).Davis also teaches detectors configured to perform Raman spectroscopy because Raman scattering labels are detected (paragraph 0054). Davis also teaches the immobilized nucleic acid provides the added advantage of allowing genotyping of the target nucleic acid (paragraph 0052), which aids in the detection of genetic diseases. Thus, Davis teaches the known technique of using immobilized non-aptameric nucleic acids (i.e., claim 45) and a polymerase and primer (i.e., claim 52).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising immobilized nucleic acids as taught by Shipwash so that the device comprises the

immobilized non-aptameric nucleic acid (i.e., claim 45) and the polymerase and primer in the chamber (i.e., claim 52) as taught by Davis to arrive at the claimed apparatus with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in an apparatus having the added advantage of aiding in the detection of genetic diseases as a result of allowing genotyping of the unknown target nucleic acid as explicitly taught by Davis (paragraph 0054). In addition, it would have been obvious to the ordinary artisan that the known technique of using the nucleic acids, polymerase, and primer of Davis could have been applied to the apparatus of Shipwash with predictable results because the known technique of using the nucleic acids, polymerase, and primer of Davis predictably results in immobilized molecules suitable for analysis for genetic diseases.

Shipwash also teaches each Raman detection unit is capable of detecting at least one nucleotide at the single molecule level; namely, single molecule detection is performed (paragraph 0168). Nucleotides are molecules; thus, because single molecule detection is performed, and because nucleotides are molecules, Shipwash teaches a unit capable of detecting a nucleotide at the single molecule level. Shipwash also teaches nucleic acids are on metal particles in channels (paragraph 0043), which is interpreted as being in the inlet and outlet channels. However, neither Shipwash nor Davis teach the Raman detection units configured for surface enhanced Raman spectroscopy or the detection of at least one unlabeled nucleotide at a single nucleotide level, nor do Shipwash or Davis teach surface enhanced Raman spectroscopy active particles that are not labels.

However, Chan et al teaches Raman detection units configured for surface enhanced Raman spectroscopy of nucleotides (paragraph 0072), wherein the detection units detect single unlabeled nucleotides, wherein the detectors have the added advantage of specifically identifying the nucleotide (paragraph 0096) for the purpose of sequencing a nucleic acid (Abstract), which aids in the detection of genetic diseases. Chan et al teach channels packed with SERS nanoparticles (Abstract), which have the added advantage of enhancing the detection of the Raman signal from the nucleotides (paragraph 0010). Thus, Chan et al teach the known technique of using detection units configured for surface enhanced Raman spectroscopy detection of single unlabeled nucleotides and the known technique of using channels packed with SERS nanoparticles.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising two Raman detection units of Shipwash in view of Davis so that the detection units are the detection units configured for surface enhanced Raman spectroscopy detection of single unlabeled nucleotides, and so that the outlet channel comprises SERS nanoparticles as taught by Chan et al to arrive at the instantly claimed apparatus with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in an apparatus having the added advantage of aiding in the detection of genetic diseases as a result of allowing specific identification of a nucleotide) for the purpose of sequencing a nucleic acid as taught by Chan et al (Abstract and paragraph 0096), as well as having

the additional added advantage of enhancing the detection of the Raman signal from the nucleotides as taught by Chan et al (paragraph 0010). In addition, it would have been obvious to the ordinary artisan that the known detection units and SERS nanoparticle packed channels of Chan et al could have been used in the apparatus of Shipwash in view of Davis with predictable results because the known detection units and SERS nanoparticle packed channels of Chan et al predictably result in detectors and channels usable for detecting nucleotides.

Regarding claim 47, the apparatus of claim 45 is discussed above. Shipwash also teaches the concentrations of nucleotides are measured by Raman spectroscopy as they flow through the outlet channel; namely, the system detects concentration (paragraph 0170) and uses Raman spectroscopy (paragraph 0174).

In addition, as noted above, apparatus claims cover what a device *is*, not what a device *does*. Therefore, the various uses recited in claim 47 (e.g., measuring concentration of nucleotides) fail to define additional structural elements to the device of claim 47. Because the prior art teaches the structural elements of claim 47, claim 47 is obvious over the prior art.

Regarding claim 48, the apparatus of claim 45 is discussed above. Shipwash also teaches the inlet channel and outlet channel diameter is between about 100 and about 200 micrometers in diameter (paragraph 0210).

Regarding claim 53, Shipwash teaches an apparatus. In a single exemplary embodiment, Shipwash teaches a reaction chamber containing a single template nucleic acid molecule attached to an immobilization surface; namely, a mixing channel,

which is a reaction chamber, further comprising a bead having nucleic acids immobilized thereon (Figures 11 and 14, and paragraphs 0066 and 0255). The apparatus of Shipwash further comprises an inlet channel in fluid communication with the reaction chamber; namely, Figure 9, wherein the inlet channel comprises the channel having the digestion chamber (Figure 9), which is separate and distinct from the reaction chamber because the chamber is separate (paragraph 0043). Shipwash also teaches the apparatus comprises a separate and distinct outlet channel in fluid communication with the reaction chamber; namely, Figure 9 show an outlet channel is separate and downstream of the reaction chamber.

Shipwash also teaches a first Raman detection unit operably coupled to the reaction chamber; namely, a detector is coupled to the reaction chamber above the portion marked "outlet" of Figure 9. A review of the specification yields a recitation in paragraph 0033 that the reaction chamber has "subcompartments." Thus, the narrow portion of Figure 9 having the detector that is downstream as well as the upstream portions labeled "reaction chamber" and mixer in Figure 9 are collectively interpreted as the "subcompartments" that comprise the claimed "reaction chamber," and the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding a "reaction chamber" (*In re Hyatt*, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1]). Shipwash also teaches the concentrations of nucleotides are measured by Raman spectroscopy in the reaction chamber; namely, the system detects concentration (paragraph 0031) and uses Raman spectroscopy (paragraph 0174), and the detector is coupled to the reaction chamber as

described above. The first Raman detection unit detects the concentrations without background signals form the nucleic acid because the first Raman detection unit is downstream from the portion of reaction chamber having the immobilized nucleic acids (Figure 9).

As noted above, apparatus claims cover what a device *is*, not what a device *does*. In particular, it is noted that claim 53 does not actually require nucleotides anywhere in the apparatus. Thus, because the various uses recited in claim 53 (e.g., measuring concentration of nucleotides) fail to define additional structural elements to the device of claim 53, the claim is obvious over the prior art.

While Shipwash also teaches detection of binding to an oligonucleotide aptamer (paragraph 0155), Shipwash does not teach a non-aptameric immobilized nucleic acid.

However, Davis teaches an apparatus comprising a reaction chamber containing a template comprising nucleic acid molecule attached to an immobilization surface; namely, an immobilized complex comprising a target (i.e., non-aptameric) nucleic acid (paragraph 0057). Davis also teaches the immobilized nucleic acid provides the added advantage of allowing genotyping of the target nucleic acid (paragraph 0052), which aids in the detection of genetic diseases. Thus, Davis teaches the known technique of using immobilized non-aptameric nucleic acids.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising immobilized nucleic acids as taught by Shipwash so that the device comprises the immobilized non-aptameric nucleic acid as taught by Davis to arrive at the claimed

apparatus with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in an apparatus having the added advantage of aiding in the detection of genetic diseases as a result of allowing genotyping of the unknown target nucleic acid as explicitly taught by Davis (paragraph 0054). In addition, it would have been obvious to the ordinary artisan that the known technique of using the non-aptameric nucleic acid of Davis could have been applied to the apparatus of Shipwash with predictable results because the known technique of using the non-aptameric nucleic acid of Davis predictably results in immobilized molecules suitable for analysis for genetic diseases.

Shipwash also teaches the Raman detection unit is capable of detecting at least one nucleotide at the single molecule level; namely, single molecule detection is performed (paragraph 0168). Nucleotides are molecules; thus, because single molecule detection is performed, and because nucleotides are molecules, Shipwash teaches a unit capable of detecting a nucleotide at the single molecule level. However, neither Shipwash nor Davis teach the Raman detection units configured for the detection of at least one unlabeled nucleotide at a single nucleotide level.

However, Chan et al teaches Raman detection units configured for surface enhanced Raman spectroscopy of nucleotides (paragraph 0072), wherein the detection units detect single unlabeled nucleotides, wherein the detectors have the added advantage of specifically identifying the nucleotide (paragraph 0096) for the purpose of sequencing a nucleic acid (Abstract), which aids in the detection of genetic diseases.

Thus, Chan et al teach the known technique of using detection units configured for surface enhanced Raman spectroscopy detection of single unlabeled nucleotides.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising a Raman detection unit of Shipwash in view of Davis so that the detection unit is the detection unit configured for surface enhanced Raman spectroscopy detection of single unlabeled nucleotides as taught by Chan et al to arrive at the instantly claimed apparatus with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in an apparatus having the added advantage of aiding in the detection of genetic diseases as a result of allowing specific identification of a nucleotide) for the purpose of sequencing a nucleic acid as taught by Chan et al (Abstract and paragraph 0096). In addition, it would have been obvious to the ordinary artisan that the known detection unit of Chan et al could have been used in the apparatus of Shipwash in view of Davis with predictable results because the known detection unit of Chan et al predictably result in a detector usable for detecting nucleotides.

Regarding claim 54, the apparatus of claim 53 is discussed above. Shipwash also teaches a second Raman detection unit operably coupled to the inlet channel; namely, an optical detector is integrated onto the inlet digestion chamber (paragraph 0484), wherein Raman spectroscopy is used (paragraph 0174); thus, the second optical detector is a Raman detection unit.

Regarding claim 55, the apparatus of claim 53 is discussed above. Shipwash also teaches a mixer operably coupled to the reaction chamber; namely, the narrow portion of Figure 9 having the detector that is downstream as well as the upstream portions labeled "reaction chamber" and mixer in Figure 9 are collectively interpreted as the "subcompartments" that comprise the claimed "reaction chamber" as described above.

10. Claims 23 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shipwash (U.S. Patent Application Publication No. US 2002/0058273 A1, published 16 May 2002) in view of Davis (U.S. Patent Application Publication No US 2002/0102595 A1, published 1 August 2002) in view of Chan et al (U.S. Patent Application No. US 2003/0187237 A1, published 2 October 2003, filed 26 March 2002) as applied to claims 18 and 36 above, and further in view of Ogle (U.S. Patent No. 6,328,869 B1, issued 11 December 2001).

Regarding claims 23 and 40, the apparatus of claims 18 and 36 is discussed above in Section 9.

While Shipwash also teaches the apparatus further comprises a mesh in the form of filters and grids that retain nanoparticles in the channels of the apparatus (paragraphs 0167 and 0270), and that metals are used to make the substrates for the apparatus (paragraph 0164), Shipwash, Davis, and Chan et al are silent with respect to the materials used for the mesh.

However, Ogle teaches an apparatus for macromolecule purification (Title) comprising a mesh comprising platinum; namely, a platinum-coated titanium expanded mesh, which has the added advantage of being self supported and inexpensive (column 8, lines 50-62). Thus, Ogle teaches the known technique of using a mesh comprising platinum.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising a mesh as taught by Shipwash in view of Davis and Chan et al so that the mesh is the platinum mesh of Ogle to arrive at the instantly claimed apparatus with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in an apparatus having the added advantage of being self supported and inexpensive as explicitly taught by Ogle (column 8, lines 50-62). In addition, it would have been obvious to the ordinary artisan that the known technique of using the platinum mesh of Ogle could have been applied as the mesh of the apparatus as taught by Shipwash in view of Davis and Chan et al with predictable results because the platinum mesh of Ogle predictably results in a mesh suitable for the filtration of biological macromolecules.

Response to Arguments

11. Applicant's arguments filed in the Remarks have been fully considered but they are not persuasive for the reason(s) listed below.

A. Applicant argues on page 13 of the Remarks that none of the cited references teaches a difference between the first concentration of nucleotide and the second concentration of nucleotide is proportional to the amount of nucleotide incorporated in a newly synthesized strand complementary to the nucleic acid.

However, as detailed in the rejections above, Davis teaches the target nucleic acid is subjected to sequencing by adding and detecting nucleotides upstream of the immobilized complex and detecting the presence of absence of the nucleotides downstream from the immobilized complex, and that the concentrations of the nucleotides (i.e., NTPs) are tracked (paragraph 0006-0009); thus, upon incorporation of a nucleotide using the immobilized nucleic acid, polymerase and primer, a different (i.e., second) concentration of nucleotide is detected compared to the original (i.e., first) concentration of nucleotide detected upstream. The concentration difference is proportional to the amount of nucleotide incorporated into a newly synthesized strand because a polymerase extends a primer using the nucleotides (paragraph 0006-0009). Davis also teaches first and second illumination zones that are respectively upstream and downstream of the immobilized complex (paragraph 0006), wherein the first and second illumination zones each have a detection device operably coupled thereto (claim 15 of Davis). The detectors are configured to perform Raman spectroscopy because Raman scattering labels are detected (paragraph 0054). Davis also teaches the first and second concentration of nucleotides and the immobilized nucleic acid provide the added advantage of allowing genotyping of the target nucleic acid (paragraph 0052), which aids in the detection of genetic diseases. Thus, Davis teaches the known

technique of using immobilized nucleic acids and first and second concentrations of nucleotides in the upstream and downstream of the immobilized nucleic acid .

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising immobilized nucleic acids as taught by Shipwash so that the device comprises the immobilized non-aptameric nucleic acid, polymerase, and primer and the two different upstream and downstream concentrations of nucleotides as taught by Davis. The modification would result in the first concentration of nucleotide being detected upstream of the reaction chamber and the second concentration being detected downstream of the reaction chamber as taught by Davis; thus, because the first Raman detector of Shipwash is coupled to the inlet channel and the second Raman detector of Shipwash is coupled to the outlet channel, the modification results in the first and second concentrations being in the inlet and outlet channels, respectively, thus arriving at the claimed apparatus with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in an apparatus having the added advantage of aiding in the detection of genetic diseases as a result of allowing genotyping of the unknown target nucleic acid as explicitly taught by Davis (paragraph 0054). In addition, it would have been obvious to the ordinary artisan that the known technique of using the nucleic acids, nucleotide concentrations, and polymerase and primer of Davis could have been applied to the apparatus of Shipwash with predictable results because the known technique of using

the nucleic acids, nucleotide concentrations, and polymerase and primer of Davis predictably result in immobilized molecules suitable for analysis for genetic diseases.

In addition, it is noted that only claim 18 actually requires the first and second concentrations of nucleotides. Therefore, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the first and second concentrations) are not recited in the rejected independent claims 36, 51, 45, and 53. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Therefore, as detailed above, the limitations regarding measuring of concentrations in claims 36, 51, 45, and 53 clearly describe an intended sue of the claimed apparatus, and do not define additional structural elements to the claimed device. Thus, for the reasons detailed above, the claims are obvious over the prior art.

B. Applicant argues on page 14 of the Remarks that the detection of a single unlabeled nucleotide molecule would have been totally unexpected at the time of the invention.

However, as noted above, Chan et al clearly teaches Raman detection units configured for surface enhanced Raman spectroscopy of nucleotides (paragraph 0072), wherein the detection units detect single unlabeled nucleotides, wherein the detectors have the added advantage of specifically identifying the nucleotide (paragraph 0096) for the purpose of sequencing a nucleic acid (Abstract), which aids in the detection of genetic diseases. Thus, Chan et al teach the known technique of using detection units

configured for surface enhanced Raman spectroscopy detection of single unlabeled nucleotides, and the modification of the device of Shipwash in view of Davis would clearly have been obvious to the ordinarily skilled artisan at the time the claimed invention was made for the reasons presented in the rejections above.

C. Applicant's remaining arguments with respect to the previous rejections of the claims have been considered but are moot in view of the new ground(s) of rejection necessitated by the amendments.

Conclusion

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

14. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571)272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert T. Crow/
Examiner, Art Unit 1634

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/Diana B. Johannsen/
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